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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL2006/001174	15.10.2006	11.10.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07K5/06 A61L27/52 A61L27/38 A61L27/22

Applicant
RAMOT AT TEL AVIV UNIVERSITY LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Hars, Jesko Telephone No. +49 89 2399-7825

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL2006/001174

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 33,34 (partially)

because:

☒ the said international application, or the said claims Nos. 33,34 (partially) relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 33,34 (partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL2006/001174

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	13,30-34
	No:	Claims	1-12,14-29,35-41
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12,14-41
Industrial applicability (IA)	Yes:	Claims	1-33,36-41
	No:	Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

D1: MAHLER A, RECHES M, GAZIT E ET AL.: "Rigid, Self-Assembled Hydrogel Composed of a Modified Aromatic Dipeptide" ADVANCED MATERIALS, vol. 18, 25 April 2006 (2006-04-25), pages 1370-1365, XP002446150

D2: JAYAWARNA V, ULIJN R ET AL.: "Nanostructured Hydrogels for Three-Dimensional Cell Culture Through Self-Assembly of Fluorenylmethoxycarbonyl? Dipeptides" ADVANCED MATERIALS, vol. 18, 2 March 2006 (2006-03-02), pages 611-614, XP002446151

D3: TOLEDANO SOPHIE ET AL: "Enzyme-triggered self-assembly of peptide hydrogels via reversed hydrolysis" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 128, no. 4, 1 February 2006 (2006-02-01), pages 1070-1071, XP002421984 ISSN: 0002-7863

D4: WO 2007/029003 A (UNIV MANCHESTER [GB]; ULIJN REIN VINCENT [GB]; TOLEDANO SOPHIE [FR]) 15 March 2007 (2007-03-15)

D5: RECHES M ET AL: "Casting metal nanowires within discrete self-assembled peptide nanotubes" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 300, no. 5619, 25 April 2003 (2003-04-25), pages 625-627, XP002276672 ISSN: 0036-8075

D6: Online Supporting Material to D5

D7: RECHES M ET AL: "Self-Assembly of Peptide Nanotubes and Amyloid-like Structures by Charged-Termini-Capped Diphenylalanine Peptide Analogues" ISRAEL JOURNAL OF CHEMISTRY, vol. 45, no. 3, 30 June 2005 (2005-06-30), pages 363-371, XP009087914 cited in the application

D8: ZHANG YAN ET AL: "Supramolecular hydrogels respond to ligand-receptor interaction" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 125, no. 45, 12 November 2003 (2003-11-12), pages 13680-13681, XP002421981 ISSN: 0002-7863 cited in the application

D9: HOLMES TODD C ET AL: "Extensive neurite outgrowth and active synapse formation on self-assembling peptide scaffolds" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC, US, vol. 97, no. 12, 6 June 2000 (2000-06-06), pages 6728-6733, XP002213924 ISSN: 0027-8424 cited in the application

D10: YOKOI HIDENORI ET AL: "Dynamic reassembly of peptide RADA16

nanofiber scaffold" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 102, no. 24, June 2005 (2005-06), pages 8414-8419, XP002446152 ISSN: 0027-8424

D11: RECHES M ET AL: "Amyloid fibril formation by pentapeptide and tetrapeptide fragments of human calcitonin" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOCHEMICAL BIOLOGISTS, BIRMINGHAM,, US, vol. 277, no. 38, 20 September 2002 (2002-09-20), pages 35475-35480, XP002276670 ISSN: 0021-9258

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 33,34 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 INVENTION

The inventors had previously reported the self-assembly of diphenylalanine (FF), which is the aromatic core of beta-amyloid peptide, into a novel class of peptide nanotubes. Similar structures could be obtained with Boc-FF-COOH, Z-FF-COOH and Fmoc-FF. The "unique" Fmoc-FF intriguingly formed fibrillar structures very similar to amyloid fibrils formed by much longer peptides - Fmoc-FF is thus the smallest building block for amyloid-like fibrils.

The inventors have found now that in "diluted aqueous solutions" (present application") / "at a higher concentration" (article of invention), a hydrogel instead of peptide nanotubes is formed, characterised through a network of fibrils of 10-100 nm.

Stock solutions (HFIP as solvent) of peptide were added to water at a final

concentration of 0.5, 1, 2, 5, 10 mg/mL (claims are limited to 0.1-50 mg/mL). The hydrogels self-assembled at room temperature, were strong, rigid and stable at a broad temperature range and resisting acid and basic attack, with strength and rigidity increasing with concentration in the range of 2-10 mg/mL. The gels were much stronger than other self-assembled peptide hydrogels (mentioned are those of Zhang and the RADA-gels of Holmes).
The inventors attribute the strength of the gel to the beta-sheet structure established by the aromatic groups (Pi-stacking) of the Fmoc-FF, as opposed to the RADA-gels which build a beta-sheet out of ionic interactions only.
The gel, while assembling, can be injected and brought into any shape, which makes it useful for injection into a target site.
They went on to test the hydrogel for its ability to store drugs in its microcavitities and to use it as a tissue culture scaffold, culturing CHO cells. Both tests were satisfactorily.

Priority of the present application
The RO was the Israel Patent Office, which was closed from 08-12 oct 2006 for holidays, and on 13 and 14 oct 2006 for the weekend (Friday and Saturday). The first priority is thus formally validly claimed.

The claims relate to subject-matter with the following **effective dates**:
11.10.2005: claims 10,11,16-22,26,27,29
23.03.2006: claims 1-9,12-15,23-25,28,30,31,35-39
15.10.2006: claims 32-34,40,41

V.2 CLARITY, SUFFICIENCY OF DISCLOSURE

Fmoc-FF is generalised in the claims to a peptide that is up to 6 aas long, comprising at least one aromatic aa. Its minimum length of 2 aas on p21L4-5 is only optional, ie it can be just one amino acid. The examples are confined to Fmoc-FF. In previous publications, the inventors have also limited their experiments to diphenylalanine peptide (Boc-FF, Z-FF). In the article of the invention, Fmoc-FF is characterised as "unique" since it forms amyloid-like fibrils, unlike Boc-FF or Z-FF. On p2L19-23, it is repeated that only Fmoc-FF can build those fibrils, and that it represents the "smallest structural unit that can form typical amyloid-like fibrils".
Both in the case of the fibrils (p2L10-14) and in the case of the hydrogels of the present application (article of invention, p1367, right col, §1) the inventors believe that Pi-stacking interactions between the aromatic aas are form beta-sheets, ie the

interactions are the same.
If Fmoc-FF is the "smallest" "unique" building block for amyloid-like fibrils characterised by the same molecular interactions as the present hydrogels, it can be assumed prima facie that the hydrogels can only be built by using Fmoc-FF.
Further evidence is provided by XP002276672 (from 2003), an earlier publication by the inventors: Stock solutions (HFIP as solvent) of peptides were added to water at a final concentration of 2 mg/mL. A 1-day-aged solution of the peptides was then TEM-analysed.
The individual peptides analysed were: FF (fig.1B, article) WW, WY, WF (fig.S3, Supporting Online Material). Concentrations of 0.01 - 0.5 mg/mL were also prepared. The concentrations used were thus those well falling into the range at which Fmoc-FF forms a hydrogel. 1-day-aged aqueous solutions should have developed the hydrogel, if that was possible.
No observation was made of any formed hydrogel. In the article of the invention, it is stated that the observation of a spontaneously forming hydrogel was only made when dissolving Fmoc-FF.
It seems as if Fmoc-FF indeed is not only a unique dipeptide capable of forming amyloid-like structures, but also a unique dipeptide capable of forming the self-assembling hydrogels based on Pi-stacking.
The inventors have further published in D7 that only the peptides Fmoc-FF and Cbz-FF with their aromatic end cap, but not Boc-FF with its non-aromatic end cap, formed amyloid-like unordered fibrils of a smaller diameter instead of the highly ordered nanotubes of a higher diameter observed for Boc-FF, FF, NH2-FF-NH2 and Ac-FF-NH2. Again, all peptides were dissolved in water at a concentration of 2mg/mL. The present application only discloses that Fmoc-FF develops a hydrogel. It can be assumed that the inventors would have observed if Cbz-FF or the other peptides of D7 self-assembled into hydrogels - and that they would have included this in the present application - however, no experiments relating to Cbz-FF or peptides other than Fmoc-FF are given in the present application. This is another indicator that out of the peptides Fmoc-FF, Boc-FF, FF, NH2-FF-NH2 and Ac-FF-NH2 only Fmoc-FF forms hydrogels.
XP002421984 - Toledano et al. discloses that Fmoc-FFF, Fmoc-AFF, Fmoc-VFF and Fmoc-LFF form hydrogels, but Fmoc-PFF and Fmoc-GFF did not. Nothing is said about the stability and rigidity of the formed gels, but for Fmoc-FFF Pi-stacking was observed. It can be concluded that Fmoc alone is not sufficient to obtain a hydrogel from a tripeptide.
Jayawarna, Ulijn et al. discloses that Fmoc-GF did not form a hydrogel.
In conclusion, the prior art demonstrated that FF, WW, WY, WF, Boc-FF, Z-FF,

Fmoc-PFF, Fmoc-GFF and Fmoc-GF do not form hydrogels. No monopeptide has been shown to form a hydrogel. All these peptides are currently covered by claim 1.
Leaving it to the skilled person to determine which peptides indeed form a hydrogel requires him to apply inventive step.
The generalisation made by claim 1 is thus unfounded, and the claims cover embodiments which are not disclosed in the application as filed in a manner sufficient for the skilled person to realise them, and those embodiments also lack technical support in the application.
Art. 5 and 6 PCT are contravened.
It appears that the claims need to be limited to:
- dipeptides,
- having the amino acid sequence FF,
- with the end capping Fmoc,
- ie limit the claims to Fmoc-FF.
NB: A limitation to Fmoc di or tripeptides having at least two phenylalanines would go beyond the application as filed - and it would still cover embodiments which do not work, see XP002421984.

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D4 is not mentioned in the description, nor are these documents identified therein.

The vague and imprecise statement in the description on page 50, last § ("spirit and scope") implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them.

The applicant should delete all occurences of the relative term 'about', where this term refers to a range or to range limits.
Further the applicant should delete all statements similar to 'incorporated herein by reference' - see last page of the description.

V.3 PRIOR ART

If not otherwise specified, subject matter of cited documents relates to the passages indicated in the search report.

D1 - "ARTICLE of INVENTION" - Mahler, Reches, Gazit et al., (2006) Adv. Mater. 18, 1365-1370, published online 25.04.2006 - intermediate document
The inventors had previously reported the self-assembly of diphenylalanine (FF), which is the aromatic core of beta-amyloid peptide, into a novel class of peptide nanotubes. Similar structures could be obtained with Boc-FF-COOH, Z-FF-COOH and Fmoc-FF. The "unique" Fmoc-FF intriguingly formed fibrillar structures very similar to amyloid fibrils formed by much longer peptides - Fmoc-FF is thus the smallest building block for amyloid-like fibrils.
The inventors have found now that in "diluted aqueous solutions" (present application") / "at a higher concentration" (article of invention), a hydrogel instead of peptide nanotubes is formed, characterised through a network of fibrils of 10-100 nm.
Stock solutions (HFIP as solvent) of peptide were added to water at a final concentration of 0.5, 1, 2, 5, 10 mg/mL. The hydrogels self-assembled at room temperature, were strong, rigid and stable at a broad temperature range and resisting acid and basic attack, with strength and rigidity increasing with concentration in the range of 2-10 mg/mL. The gels were much stronger than other self-assembled peptide hydrogels (mentioned are those of Zhang and the RADA gels of Holmes).
The inventors attribute the strength of the gel to the beta-sheet structure established by the aromatic groups (Pi-stacking) of the Fmoc-FF, as opposed to the RADA-gels which build a beta-sheet out of ionic interactions only.
The gel, while assembling, can be injected and brought into any shape, which makes it useful for injection into a target site.
They went on to test the hydrogel for its ability to store drugs in its microcavitities and to use it as a tissue culture scaffold, culturing CHO cells. Both tests were satisfactorily.
XP002421984 - Toledano et al. is cited in the very last § of this article.

This document appears to be relevant for inventive step of claims 32-34,40,41.

D2 - Jayawarna, Ulijn et al. (2006) Adv. Mater. 18, 611-614, published online: 02.03.2006 - intermediate document
Disclosed are self-assembling hydrogels made from the Fmoc-dipeptides Fmoc-FF, Fmoc-AG, FMoc-AA, Fmoc-LG, Fmoc-FG, Fmoc-FF. Fmoc-GF did not form a hydrogel. The authors conclude that variations in the building blocks can result in dramatic changes in self-assembled materials.
The gels were formed through suspending the peptides in water, increasing the pH to >8, which resulted in a clear solution (ie total dissolution), and dropwise lowering of the pH. Fmoc-FF hydrogels formed at pH <8, while the other hydrogels needed pH<4. Fiber

diameter is recorded for each hydrogel, and is always in the range of 10-100 nm. Concentrations at which hydrogels formed ranged from 2.2 mg/mL to 2.14 mg/mL in the case of Fmoc-FF. The hydrogels were based on Pi-stacking interactions. Bovine chondrocytes were succesfully cultured on Fmoc-FF.
The hydrogels can be used in 3D cell culture or in tissue engineering.

This document appears to be relevant for novelty for claims 1-9,12,14,15,23-25,28,35-41.
It further appears to be relevant for inventive step of claims 30-34.

D3 - XP002421984 - Toledano, Ulijn et al., published online 04.01.2006 - intermediate document
Cited is XP002421981: small Fmoc peptides self-assemble into nanofibrous structures driven by Pi-stacking.
Disclosed is the enzyme-triggered self-assembly of a Fmoc-FFF hydrogel through reverse hydrolysis of Phe-Phe with Fmoc-Phe or Fmoc-(G/A/V/L/P) (precursors). Precursors were suspended in water at <1% w/w. Before enzyme addition, no gelation was observed. After enzyme addition, self-assembly into a hydrogel occured at 37°C and 0.15 M phosphate buffered saline solution, making the system a valuable tool as a tissue scaffold that builds after injection into a site together with cells. The Fmoc-FFF hydrogel revealed interwoven fibers of approximately 10-20 nm in diameter.
At the concentrations used, Phe-Phe in the aqueous system did not form nanotubular structures, nor did it gel.

This document appears to be relevant for novelty for claims 1-7,12,15,23-25,28,35-41.
It further appears to be relevant for inventive step of claims 13,30,31.

D4 - WO2007029003 - Toledano, Ulijn et al.
This patent application corresponds to XP002421984 and discloses its results.
Further experiments involve Cbz-F with FF, the culture of bovine chondrocytes and human mesenchymal stem cells (hMSC) on Fmoc-FFF. Medical use as tissue scaffold, etc. is claimed in extensis.
Fmoc-FF as a hydrogel forming peptide is mentioned on p17L19-22, p19L8-9, p26L20, but the examples only include Fmoc-FFF. Enzyme reactions were carried out at 22°C (p40, last §).

The priority of this document is valid for Fmoc-FFF and Fmoc-FF, but not for Cbz-FFF.

Priority document: Hydrogels prepared from Fmoc-FF are disclosed on p18L1-4, p19L23-24, p26L4, but the examples only include Fmoc-FFF. Enzyme reactions were carried out at 22°C (p41L20).
The experiment using the hMSC was not described in the priority document.
The priority document, a British application, does contain claims.
The effective date for Fmoc-FFF and Fmoc-FF hydrogels of this disclosure is thus 07.09.2005.

Note that the group of Ulijn backed up the claim on Fmoc-FF later by publishing experiments in D2.

This document appears to be relevant for novelty for the claims 1-12,14-29,35-41.

D5 - XP002276672 - same inventors
Both FF and D-FF (MW: 165 g/mol) were prepared in HFIP stock solutions. When diluting them in water at a final uM concentration, within seconds nanotubes were formed.
FW, WY, WF, WW were also tested. Nanotubes were observed only for FW, with substantial amounts of amorphous aggregates.
D6 - Supporting Online Material for D5
Downloaded from http://www.sciencemag.org/cgi/data/300/5619/625/DC1/1, as indicated in D5.
Stock solutions (HFIP as solvent) of peptides were added to water at a final concentration of 2 mg/mL. A 1-day-aged solution of the peptides was then TEM-analysed.
The individual peptides analysed were: FF (fig.1B, article) WW, WY, WF (fig.S3, Supporting Online Material).
Concentrations of 0.01 - 0.5 mg/mL were also prepared.
D5 and D6 are considered to form one single disclosure, "D5+D6".

D7 - Reches et al., same inventors, cited on p2, Israel J. Chem. 45, 363-371 (30-06-2005)
Fmoc-FF and Z-FF (= Cbz-FF) (both aromatic end-cap) form amyloid-like fibrillar, ie unorderd structures of a significantly smaller diameter than the nanotubes of FF, Ac-FF-NH2 or NH2-FF-NH2.
Boc-FF (non-aromatic end-cap) formed the ordered nanotubes.
The authors concluded that some of the modified peptides might have a completely

different molecular conformation of the amide bond.
The different packing of Fmoc-FF and Cbz-FF compared to the other peptides is attributed to the additional aromatic moiety introduced with the end-cap.
All peptides were provided in stock solutions at 100 mg/mL. Stock solutions were then diluted with water to a final peptide concentration of 2 mg/mL for all peptides, apart for NH2-FF-NH2, which was diluted only to 10 mg/mL.

D8 - XP002421981 - cited on page 3 - Zhang et al.
Disclosed are self-assembling hydrogels formed by Fmoc-D-Ala-D-Ala, Fmoc-AA, Fmoc-GG, Fmoc-Gly-D-Ala, Fmoc-Gly-Thr. They require concentrations in the mM range and Fmoc-D-Ala-D-Ala undergoes a gel-sol transition upon ligation to vancomycin - which Fmoc-AA does not.
In the hydrogel phase, Pi-stacking between the Fmoc-aromatic groups occurs.

D9 - XP002213924 - cited on page 3 - Homes et al.
Disclosed are self-assembling peptide hydrogel scaffolds for tissue engineering. One peptide used is AcN-RADARADARADARADA-CNH2 (RADA16-I).
The hydrogel is used as a scaffold for extensive neurite outgrowth.

D10 - PREV200510154815 - Yokoi, Zhang et al., 2005 (14-06-2005)
Disclosed is further work on the RADA16-I peptide: It forms stable nanofibers, but also forms higher-order nanofiber scaffolds, viz. hydrogels with a water content of > 99.5 wt/vol%.
Biological molecules can be distributed therein.
It builds beta-sheets, that are stacked through opposing ionic interactions, forming the hydrogel.

D11 - XP002276670
The pentapeptide DFNKF and its shortened version DFNK form amyloid-like fibrils.
Hydrogels are not mentioned.

V.4 NOVELTY

Remarks under Art. 33(2) PCT

Features inherent to the Fmoc-FF hydrogel (see claims 16-22) cannot confer novelty even if they are not mentioned in WO2007029003.

Claim 40 covers a kit which comprises a peptide stock solution together with an aqueous solution as a functional combination. The alm to form a hydrogel by mixing the two ingredients cannot confirm novelty, only the functional combination can, ie any functional combination of these two ingredients disclosed in the art destroy the novelty.

Document D2 anticipates claims 1-9,12,14,15,23-25,28,35-41 (intermediate document).
Document D3 anticipates claims 1-7,12,15,23-25,28,35-41 (intermediate document).
Document D4 anticipates claims 1-12,14-29,35-41 (intermediate document).
Document D7 anticipates claim 40.

Claims 1-12,14-29,35-41 therefore appear to be not novel.

V.5 INVENTIVE STEP

Remarks under Art. 33(3) PCT

Concerning claims 30-34, D2, an intermediate document, is relevant art for the assessment of inventive step, given the priority situation.

Over the disclosure of D2, the subject-matter of claims 32-34 becomes immediately obvious, given that D2 talks in length of the biomedical applications of the disclosed hydrogels.

Providing a stock solution of Fmoc-FF in an organic solvent instead of simply adding the peptide as a solid to an aqueous solution cannot confer an inventive step (claims 30,31). The solvent hexafluoroisopropanol (HFIP) has been used routinely in 2003 for the peptide FF (see D5+D6).

Claims 30-34 thus appear obvious over D2 and D5+D6.

Claim 13 relates to substituted phenyl residues. These embodiments are considered to find neither support nor sufficient disclosure in the application (compare section V.2 above).
No inventive step argumentation is thus necessary.